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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,867	12/28/2000	Steven Alan Dunham	5934-01-EMA	5272

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,867	DUNHAM ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8-14 and 16-36* is/are pending in the application.

4a) Of the above claim(s) *3 and 25-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,8-14,16-24 and 36* is/are rejected.

7)☒ Claim(s) *5,6,9-14,22-24 and 36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1200*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is responsive to the complying complete set of claims filed 22 October 2004. Claims 1, 5, 6, 10-14, 16-24, and 36 have been amended, claims 2, 7, and 15 have been canceled, and claims 3 and 25-35 remain withdrawn from consideration (see paragraph 3, below). Claims 1, 4-6, 8-14, 16-24 and 36 are now under consideration. Any rejections not reiterated in this action have been withdrawn.

This action is NON-FINAL.

2. It is noted that the paper and computer readable forms of the Sequence Listing filed 23 April 2004 have been entered.

Priority

3. If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35

U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its

inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

4. As noted above, applicants have not yet perfected their priority claim to provisional application 60/106,965. It is also noted that the claimed invention is not disclosed in the provisional application. For example, the provisional application does not disclose overlapping PCR products "of approximately 10 kb to approximately 15 kb" as required by each of the independent claims. Accordingly, **the effective filing date of the instant application is that of PCT application PCT/US99/22118, filed 23 September 1999.**

Election/Restrictions

5. Claims 3 and 25-35 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 22 May 2002.

Claim Objections

6. Claims 5-6, 9-14, 22-24, and 36 are objected to because of the following informalities. Claim 5 recites "resistance to a compound a comprising" rather than "a compound comprising" (see line 2). Claim 6 recites "pproximately" in line 4 (rather than "approximately"). Appropriate correction is required.

Specification

7. This application does not contain an abstract of the disclosure. It is requested that applicants provide a copy of the abstract.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 4-6, 8-14, 16-24 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-6, 8-14, 16-24 and 36 are indefinite because it is not clear whether the claim methods require the identification of "mutations" (as set forth in the preambles of each of independent claims 1, 5, and 6), or whether the claims encompass detection of a single mutation (as indicated in the finals steps of each of claims 1, 5, and 6). Clarification is required. With regard to claim 36, it is further noted that this claim also refers to a single "mutation;" accordingly, upon amending any or all of claims 1, 5, and 6, applicant should also review claim 36 and amend the claim if necessary.

Claims 1, 4, 8, 16-21, and 36 are indefinite over the recitation of the term "defined set" in claim 1 (step a)). Neither the specification nor the prior art provide a definition for this term, and it is not clear what properties might distinguish a "defined set" of PCR products from any other set of PCR products. Accordingly, it is not clear what sets of PCR products are encompassed by (or excluded from) the invention of the claims. Clarification is required.

Claims 1, 4, 8, 16-21, and 36 are indefinite over the recitation of the phrase "which encompass the complete chromosome of a wild-type strain of bacteria for which the chromosomal sequence is known" in step a) of claim 1. It is not clear whether this phrase refers back to the "defined set of overlapping PCR products," or whether it modifies the term "random point mutations" (after which it immediately appears). As it is not clear how random point mutations could "encompass the complete chromosome of a wild-type strain of bacteria for which the chromosomal sequence is known," the claims as written are vague and indefinite.

Claims 1, 4, 8, 16-21 and 36 are indefinite over the recitation of the limitation "the individual PCR products from a resistant strain isolated in step (b)" in step c) of claim 1. There is insufficient antecedent basis for the limitation, as the claim does not previously refer to said "individual PCR products." Further, it is not clear how said "individual PCR products" are obtained – for example, are they are generated from "a resistant strain isolated in step (b)," are they obtained from the "pool" of PCR products employed in step (b), etc.

Claims 1, 4, 8, 16-21, and 36 are indefinite over the recitation of the limitation "the PCR product from a resistant strain identified in step (c)" in step d) of claim 1. There is insufficient antecedent basis for this limitation. Further, the origin of this "PCR product" and the manner in which it is obtained is unclear.

Claim 4 is indefinite because it is not clear how the claim further limits claim 1, from which it depends. The claim is drawn to the "process according to Claim 1 for identifying and characterizing drug-target interactions." However, claim 1 is drawn to a

method for identifying mutations, and the text of claim 4 provides no indication as to how claim 1 is to be modified or further limited so as to result in the "identifying and characterizing" of drug-target interactions.

Claims 5, 9-14, and 36 are indefinite because it is not clear how the various steps of claim 5 relate to one another in achieving the objective of "identifying and characterizing mutations that confer resistance to a compound." First, the "allowing" step as written appears to encompass incorporation of the PCR products of the "generating" step into the chromosome of any "wild-type bacteria" (as opposed to the same wild-type strain employed in the "generating" step, such that the products could be successfully recombined so as to allow for the identification of isolates with desired novel properties lacking in the "wild-type bacteria" of the generating step). Accordingly, it is not clear how this step would contribute to accomplishing the goal of "identifying mutations that confer resistance." Further, the "isolating" and "identifying" steps of the claim have no apparent relationship to the prior two steps – the claim as written merely requires "isolating bacterial strains that demonstrate resistance to a compound" and "identifying the mutation responsible for the resistance." Clarification of the manner in which the method steps of claim 5 relate to one another is required.

Claim 9 is indefinite over the recitation of the limitation "the bacteria" in line 1 of the claim. As each of claims 5 and 6 as written recite multiple types of "bacteria," it is not clear which bacteria of the claims constitutes "the bacteria" of claim 9. Clarification is required.

Claims 6, 9, 22-24, and 36 are indefinite because it is not clear how the various steps of claim 6 relate to one another in achieving the objective of "identifying mutations that confer resistance to a compound." First, the "allowing" step as written appears to encompass incorporation of the PCR products of the "generating" step into the chromosome of any "wild-type bacteria" (as opposed to the same species employed in the "generating" step, such that the products could be successfully recombined so as to allow for the identification of isolates with the desired novel property). Accordingly, it is not clear how this step would contribute to accomplishing the goal of "identifying mutations that confer resistance." Further, the "isolating" and "identifying" steps of the claim have no apparent relationship to the prior two steps – the claim as written merely requires "isolating bacterial strains that demonstrate resistance to a compound" and "identifying the mutation responsible for the resistance." Clarification of the manner in which the method steps of claim 6 relate to one another is required.

Claims 22-24 are indefinite because it is not clear how the claims further limit claim 6, from which they depend. Particularly, as the claims refer to "a strain of bacteria which demonstrates resistance to a compound" (rather than to "the strain of bacteria" of claim 6), the relationship of the limitations of claims 22-24 to the method of claim 6 is not clear. This rejection could be overcome by amending each of claims 22-24 to recite "the strain of bacteria which demonstrates resistance to a compound."

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 5-6, 9, 22, 24, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kok et al. (Journal of Bacteriology 179(13):4270-4276 [7/1997]) in view of Minshull et al. (US Patent No. 5,837,458 [11/1998; filed 5/1996]).

Kok et al. teach a method in which the procedures of PCR mutagenesis and transformation of PCR products into cells are combined to prepare and identify novel gene variants encoding proteins with functional properties of interest (see entire reference). Kok et al. teach that their method allows for the "swift assessment and convenient analysis of a wide range of mutations caused by errors introduced by PCR" (see page 4270, right column-page 4271, left column). The method of Kok et al. comprises steps of generating *Acinetobacter pobR* gene PCR products comprising random mutations in the nucleic acid of interest, transforming said products into an *Acinetobacter* strain that facilitates rapid screening for phenotypes of interest, isolating

strains with said phenotypes, and identification of the mutation or mutations responsible for the phenotype (see entire reference, particularly pages 4271-4273).

Kok et al. do not teach the use of their method in the identification of mutations that confer resistance to a compound. Additionally, with regard to claim 5, Kok et al. do not teach the generation of PCR products meeting the length requirements of the claims which "encompass the complete chromosome" of a "wild-type bacteria strain for which the chromosomal sequence is known," and the incorporation of said products into the chromosome of "wild-type bacteria." Regarding claim 6, Kok et al. do not teach the generation of PCR products meeting the length requirements of the claims which "encompass the complete chromosome" of a "strain of bacteria which demonstrates resistance to a compound," and the incorporation of said products into the chromosome of a "wild-type bacteria."

Like Kok et al., Minshull et al. teach methods of preparing novel gene variants encoding proteins with functional properties of interest (see entire reference). The methods of Minshull et al. may comprise steps of PCR mutagenesis (see, e.g., column 5, lines 2-8), and comprise the screening of transformants for various functional properties (see entire reference, particularly columns 15-35), including antibiotic resistance (see Example III). Minshull et al. disclose the generation of variant molecules comprising entire metabolic pathways, as well as complete genomes (see column 11, line 20-column 14, line 67), and also note that starting materials may include "the whole genome of an organism that is known to have desirable metabolic properties, but for which no information localizing the genes associated with these characteristics is

available" (column 13, lines 24-30; see also column 17, lines 47-54). Minshull et al. further disclose the generation of variant fragments in the size range of 500 bp to 50 kb prior to transformation (see column 6, lines 5-20).

In view of the teachings of Minshull et al., it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kok et al. so as to have prepared and employed larger PCR products encompassing the complete chromosome of a bacterium, to have incorporated said products back into a wild-type bacterium of the same species, and to have screened transformants for functional properties of interest such as antibiotic resistance. Kok et al. note that their method is "extremely easy and efficient," and that their method should be useful in the analysis of "a wide range of chromosomal point mutations" as long as "a selection for mutations exists" (page 4276). Given that the method of Minshull et al. is more labor intensive and time consuming than that of Kok et al. (requiring, e.g., multiple rounds of recombination to product variant products – see, e.g., column 4, line 52-column 5, line 8), an ordinary artisan would have been motivated to have made such a modification for the advantage of more rapidly generating and identifying variants have the properties taught by Minshull et al.

Regarding claim 6 and claims dependent therefrom, it is again noted that Minshull et al. teach that "the whole genome of an organism" may be "known to have desirable metabolic properties.....for which no information localizing the genes associated with these characteristics is available" (column 13, lines 24-30; see also column 17, lines 47-54). Accordingly, it would have been *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made to have modified the method of Kok et al. so as to have amplified a whole genome having such a desired property, and to have transformed amplification products, screened variants, and identified mutation(s) for the advantage of identifying the mutation or mutations conferring the "desirable metabolic properties" taught by Minshull et al.

As Minshull et al. teach that variant molecules should be screened for enhanced properties "relative to a wildtype form" of the molecules (see entire reference, particularly, e.g., column 3, lines 1-3), an ordinary artisan would have been motivated to have employed a "wild-type bacteria" (as set forth in claims 5 and 6) for the advantage of readily identify such enhanced properties compared to those of a wild-type molecule or molecules. It is further noted that the teachings of Minshull et al. encompass bacteria meeting the requirements of claims 5 and 9 (see column 13, lines 31-54).

With further regard to the length requirements of the claims (for products "of approximately 10 kb to approximately 15 kb"), it is noted that such molecules fall within the range taught by Minshull et al., as set forth above. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have selected molecules of any size falling within the range taught by Minshull et al., including the sizes encompassed by the claims (see MPEP 2144.05).

Regarding claims 22 and 24, as Minshull et al. disclose increasing diversity by using "prior methods of mutagenesis" including chemical mutagens and cassette mutagenesis, the combined teachings of Kok et al. and Minshull et al. suggest the invention of the claims.

Regarding claim 36, it is again noted that Minshull et al. disclose screening for antibacterial activity (see, e.g., Example III).

13. Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kok et al. in view of Minshull et al. as applied to claims 5-6, 9, 22, 24, and 36, above, and further in view of Belland et al. (Molecular Microbiology 14(2):371-382 [1994]).

The references of Kok et al. and Minshull et al. do not teach the particular compounds of the instant claims. Belland et al. teach screening for mutations that confer resistance to the fluoroquinolone ciprofloxacin (see entire reference). As Minshull et al. suggest screening for resistance to a variety of antibiotics, and disclose the identification of genes conferring increased resistance to the antibiotic moxalactam (see Example III), it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the method of Kok et al. and Minshull et al. in view of the teachings of Belland et also as to have similarly identified mutations conferring resistance to ciprofloxacin.

14. Claims 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kok et al. in view of Minshull et al. as applied to claims 5-6, 9, 22, 24, and 36, above, and further in view of Pruna (U.S. Patent No. 5,532,239 [7/1996]).

The references of Kok et al. and Minshull et al. do not teach the particular compound of the instant claim. Pruna teach the antibiotic clinafloxacin (column 2, lines 33-40). As Minshull et al. suggest screening for resistance to a variety of antibiotics, and disclose the identification of genes conferring increased resistance to the antibiotic moxalactam (see Example III), it would have been *prima facie* obvious to one of

ordinary skill in the art to have modified the method of Kok et al. and Minshull et al. in view of the teachings of Pruna so as to have similarly identified mutations conferring resistance to clinafloxacin.

15. Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kok et al. in view of Minshull et al. as applied to claims 5-6, 9, 22, 24, and 36, above, and further in view of Ibrahim et al (U.S. Patent No. 5,145,667 [9/1992]).

The references of Kok et al. and Minshull et al. do not teach the particular compounds of the instant claims. Ibrahim et al. teach the antibiotics triclosan and DHDPE (see column 2, lines 50-60). As Minshull et al. suggest screening for resistance to a variety of antibiotics, and disclose the identification of genes conferring increased resistance to the antibiotic moxalactam (see Example III), it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the method of Kok et al. and Minshull et al. in view of the teachings of Ibrahim et al. so as to have similarly identified mutations conferring resistance to triclosan and/or DHDPE.

16. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kok et al. in view of Minshull et al. as applied to claims 5-6, 9, 22, 24, and 36, above, and further in view of Wohlstader (U.S. Patent No. 6,087,177 [7/11/2000; filed 3/16/1992]).

While Minshull et al. suggest increasing diversity by using "prior methods of mutagenesis" (including chemical mutagens and cassette mutagenesis), neither Kok et al. nor Minshull et al. disclose UV light mutagenesis. Wohlstader teaches mutation by UV irradiation (see entire reference, particularly column 24, lines 28-37). In view of the teachings of Wohlstader, it would have been *prima facie* obvious to one of ordinary skill

in the art at the time the invention was made to have modified the method of Kok et al. in view of Minshull et al. so as to have employed UV light mutagenesis, as taught by Wohlstader. The teachings of Minshull et al. are sufficient to suggest the use of any type of prior art mutagenesis method, including that of Wohlstader.

Conclusion

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen
Primary Examiner
Art Unit 1634

2/6/2006